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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/423,100 | 12/11/2000 | Zhong-Ru Gan | 20700-703 | 6340 |

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| EXAMINER | |
|---|---|
| NICHOLS, CHRISTOPHER J | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1647 | |

DATE MAILED: 12/24/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

S.17

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/423,100 | GAN, ZHONG-RU | |
| | Examiner | Art Unit | |
| | Christopher Nichols, Ph.D. | 1647 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *12 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *78-97, 99, 102-104, 113, 114, 116, 121-124, 127, 128, 136, 140, 142, and 143* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *78-97,99,102-104,116,121-123,127,128,136,142 and 143* is/are rejected.

7)☒ Claim(s) *113, 114, 124, and 140* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 December 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. §§ 119 and 120**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☒ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

### *Status of Application, Amendments, and/or Claims*

1. The Response and Amendment filed 18 August 2003 has been received and entered in full. Claims **1-77, 100, 101, 105-112, 115, 117, 118, 119, 125, 126, 129, and 130** have been cancelled. Claims **132-143** have been added.

2. Newly submitted claim **140** is directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: SEQ ID NO: 6 and SEQ ID NO: 7 were not elected nor rejoined in the previous Office Action (19 March 2003). However, upon further reconsideration, the Examiner hereby rejoins SEQ ID NO: 6 and SEQ ID NO: 7 into the currently elected invention for the purpose of a more complete description of the invention under examination.

3. The Response and Amendment filed 12 November 2003 has been received and entered in full. Claims **98, 120, 131-135, 137-139,** and **141** have been cancelled. Claims **78, 113, 114, 123, 124,** and **142** have been amended.

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

### *Withdrawn Objections And/Or Rejections*

5. The Objection to the Specification as set forth at pp. 3 ¶5 in the previous Office Action (19 March 2003) is *withdrawn* in view of Applicant's submittal of a copy of the abstract as filed (Exhibit A, 18 August 2003).

6. All previously made rejections and objections are hereby *withdrawn* in view of Applicant's amendments (18 August 2003 & 12 November 2003) and the Declaration under 37 CFR 1.132 filed 3 December 2003.

7. It is noted that said amendments and Declaration has raised new grounds for rejections for claims **78** and **123** but as a courtesy to Applicant, the rejection herein is not made Final.

***New Objections And/Or Rejections***

8. Claims **113, 114, 124,** and **140** are objected to because of the following informalities: said claims depend from rejected claims. Appropriate correction is required.

9. Claims **78, 79-97, 99, 102-104, 116, 121, 122, 123, 127, 128, 136, 142,** and **143** are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *the method of claim 78 and product of claim 123 wherein the first peptidyl fragment comprises at least the first 40 amino acids of SEQ ID NO: 1,* does not reasonably provide enablement for *peptidyl fragments shorter than the first 40 amino acids of SEQ ID NO: 1.* The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to **make** or **use** the invention commensurate in scope with these claims.

10. The claims are drawn very broadly to a product and method of using said product where the first peptidyl fragment is human Growth Hormone (hGH; SEQ ID NO: 2). The language of said claims encompasses peptides as small as 20 amino acids or as long as 92 amino acids.

11. The specification teaches that hGH can be used as a covalently linked intramolecular chaperone to improve the folding efficiency of human insulin in an *E. coli* system (Example 5;

pp. 23-26). The hGH used as the intramolecular chaperone may be as small as the first 49 amino acids of said protein (SEQ ID NO: 1).

12. Applicant has also provided a Declaration under 37 C.F.R. 1.132 demonstrating the invention using a first peptidyl fragment with only the first 40 amino acids, however, it does not lend support to the use of first peptidyl fragments shorter than the first 40 amino acids of SEQ ID NO: 1 (or SEQ ID NO: 2).

13. The specification fails to provide any guidance for the successful manufacture or use of intramolecular chaperone proteins derived from hGH that are shorter than 40 amino acids (SEQ ID NO: 1), and since resolution of the various complications in regards to characterizing a new property in a known product is highly unpredictable, one of skill in the art would have been unable to practice the invention without engaging in undue trial and error experimentation (MPEP §2112.02-2112.02). In order to practice the invention using the specification and the state of the art as outlined below, the quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of fragments of hGH to determine if they possess the necessary biological activity (MPEP §2164.01(a)).

14. While general guidance is given regarding a product with the claimed properties wherein the first peptidyl fragment is SEQ ID NO: 1, and the second peptidyl fragment is either SEQ ID NO: 4 or SEQ ID NO: 5, no working examples are given re: working mutants, variants, and fragments of SEQ ID NO: 1 with the same claimed bioactivity. In the absence of any guidance from the specification, the amount of experimentation would be undue, and one would have been unable to practice the invention over the scope claimed.

15. Additionally, a person skilled in the art would recognize that predicting the efficacy of using a hGH fragment based solely on the performance of the full-length or a 40-mer fragment as highly problematic (see MPEP §2164.02). Thus, although the specification prophetically considers and discloses general methodologies of making and using the claimed intramolecular chaperone proteins based on hGH fragments, such a disclosure would not be considered enabling since the state of protein biochemistry is highly unpredictable. As noted by the Applicant in the specification, the results from the above experiment were unexpected (pp. 2, 9-10). Thus, neither the art nor the specification gives support for use of an intramolecular chaperone other than SEQ ID NO: 1 and SEQ ID NO: 2. The factors listed below have been considered in the analysis of enablement:

(A) **The breadth of the claims;**
(B) **The nature of the invention;**
(C) **The state of the prior art;**
(D) **The level of one of ordinary skill;**
(E) **The level of predictability in the art;**
(F) **The amount of direction provided by the inventor;**
(G) **The existence of working examples; and**
(H) **The quantity of experimentation needed to make or use the invention based on the content of the disclosure.**

16. The following references are cited herein to illustrate the state of the art of protein biochemistry and intramolecular chaperones.

17. The art teaches that an exogenous peptide can be used as an activating peptide to improve the folding of a target polypeptide when the activating peptide has the amino acid sequence of the prosequence of the target polypeptide or of a polypeptide which has the same function as the target polypeptide and which is similar in amino acid sequence to the target polypeptide. US 5719021 (**IDS #AD**) discloses use of this method for target polypeptides such as

carboxypeptidase A, carboxypeptidase B, leucine aminopeptidase, N-terminal exopeptidases, pepsin, chymotrypsinogen, thrombin, prothrombin, pancreatic elastase, cathepsins, kinin-forming and kinin destroying enzymes, streptococcal proteinase, collagenases, colstripain, and renin (claims 1-23).

18. Inouye (1991) "Intramolecular Chaperone: The Role of the Pro-Peptide in Protein Folding." Enzyme **45**: 314-321 (**IDS #AH**) teaches the mutations in the pro-peptide form of subtilisin can eliminates its activity as an intramolecular chaperone (IMC). For instance, deletion of the first 14 or 43 residues on the N-terminus of pro-subtilisin eliminated its ability to function as an IMC for subtilisin (pp. 315). Also, synthetic subtilisin pro-peptides corresponding to –44 to –77, -1 to –64, and –1 to –43 are incapable of binding subtilisin and thus can not act as IMC's (pp. 316). Also, point mutations in pro- subtilisin like Gly to Arg at position –76, Met to Thr at position –60, Lys to Glu at position –45, Asp to Asn at position 32, Val to Ala at –13 eliminate the IMC activity of pro-subtilisin (pp. 316-317; Figure 1). Therefore undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

19. Thus the specification of the instant application fails to provide adequate guidance for one of skill in the art to overcome the unpredictability and challenges of applying results from examples with prophetic guidance to the practice as exemplified in the references herein.

***Summary***

20. No claims are allowed.

21. All other pending claims are objected to for depending from rejected claims.

22. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

a. US 4,665,160 (12 May 1987) Seeburg

b. Moore & Kelly (22 May 1986) "Re-routing of a secretary protein by fusion with human growth hormone sequences." Nature **321**(6068): 443-446

c. Cattini & Eberhardt (11 February 1987) "Regulated expression of chimaeric genes containing the 5'-flanking regions of human growth hormone-related genes in transiently transfected rat anterior pituitary tumor cells." Nucleic Acids Research **15**(3): 1297-1309

d. Geli *et al.* (1 August 1989) "Synthesis and sequence-specific proteolysis of a hybrid protein (colicin A::growth hormone releasing factor) produced in *Esherichia coli*." Gene **80**(1): 129-136

e. Hirt *et al.* (February 1987) "The Human Growth Hormone Gene Locus: Structure, Evolution, and Allelic Variations." DNA **6**(1): 59-70

f. Liebhaber *et al.* (25 October 1986) "Synthesis of Growth Hormone-Prolactin Chimeric Protein and Processing Mutants by the Exchange and Deletion of Genomic Exons." The Journal of Biological Chemistry **261**(30): 14301-14306

## *Conclusion*

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Christopher James Nichols, Ph.D.** whose telephone number is 703-305-3955. The examiner can normally be reached on Monday through Friday, 8:00AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Gary Kunz, Ph.D.** can be reached on 703-308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications. The fax phone numbers for the customer service center is 703-872-9305

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Elizabeth C. Kemmerer

CJN
December 3, 2003

ELIZABETH KEMMERER
PRIMARY EXAMINER